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Original Articles, Selections and Translations.

ART. I.—THE ANATOMICAL AND PHYSIOLOGICAL EFFECTS OF STRYCHNIA ON THE BRAIN, SPINAL CORD AND NERVES.

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IN an essay of the character of the present one, it is neither desirable nor necessary that equal prominence should be given to each individual question involved in the theme. Many points relating to the subject of Strychnia poisoning may be regarded as satisfactorily settled, and further than that the writer has recorded the fact that his experiments have verified the well established *dicta* of previous writers, he has devoted but little space to them.

Except in so far as it has been deemed essential to a fair contrasting of the effects of Strychnia on different classes of animals, or of different doses on species of the same class, I have not specially detailed those phenomena observed on the administration of this alkaloid, which are familiar to all. The chief interest in these phenomena, certainly does not centre in the fact that there are convulsions, *et cetera*, but in the problems which the latter suggest to the physiological logician.

Among such problems, the following are the most prominent:

I. Is there any one portion of the nervous system on which strychnia localizes, or concentrates its action?

II. If such a predilection for a special division of the nervous system exists, is the *locus predilictionis* the same in all classes of vertebrates?

III. Does strychnia produce its peculiar motor influence in any way other than the one usually accorded it, of increasing the reflex excitability?

IV. Does strychnia induce any essential pathological changes?

V. Does the action of the agents employed experimentally or therapeutically as antidotes to strychnia, depend upon a true antidotal influence (chemical antithesis), or merely on their virtue in annulling certain *results* of the poisonous action?

VI. Having determined the anatomical and physiological effects of acute strychnia poisoning, it remains for us to study what practically, at least, is of equal importance: the results of chronic strychnia poisoning.

Each of the foregoing questions involves other subsidiary ones, which will be considered in their proper connection. I have ranged the various experiments and their discussion under the head of propositions embodying the results obtained.

As the effects of strychnia are not uniform at different temperatures, it may be well to state that the experiments demonstrating the different actions of varying doses, were performed in winter, in an unheated room, whose temperature ranged from 2° to 15° C.

Unless otherwise specified, the preparation of strychnia employed has been the acetate.

PROPOSITION I.

The more the central nervous system preponderates over the scattered ganglionic centres, the more pronounced are the exalted actions of the voluntary muscles. Among vertebrates the higher we rise in the scale, the more pronounced do clonic convulsions become, as contrasted with tonic convulsions, and the more apt are we to find intervals of apparent recovery from the strychnia effects occurring. The rate of the clonic spasms differs according to the rate of rapidity of the motions of a given species under natural circumstances.

In order to compare the effects of the alkaloid on different species, I have performed a series of preliminary experiments on such animals as were accessible to me, grading the dose proportionately to the weight of the animal. Such dose gradation can be carried out with those animals only which are air-breathers, or with such water-breathers as permit of the application of the hypodermic method. With other aquatic species, the poison has been added to their respiratory medium. I append a list of the animals experimented on, as well as of their number:

1.	Equus caballus (horse)	1
2.	Canis familiaris (dog) adult	6
2.	Canis familiaris (dog) puppies	11
3.	Felis catus (cat) adult	4
3.	Felis catus (cat) kittens	10
4.	Capra hircus (goat)	1
4.	Lepus cuniculus (rabbit)	9
6.	Cavia cobaya (guinea pig)	2
7.	Vespertilio Noveboracensis (bat)	3
8.	Mus musculus	1
9.	Didelphys virginiana (opossum)	1
10.	Corvus Americanus (crow)	1
11.	Columba (pigeon)	2
12.	Alligator Mississipiensis	2
13.	Chelydra serpentina (snapping turtle)	1
14.	Chrysemys picta (painted turtle)	2
15.	Malacoclemmys palustris (terrapin)	1

16.	Nanemys guttata (sp. turtle)	3
17.	Cistudo Carolina (box-turtle)	2
18.	Rana pipiens (bull-frog)	1
19.	Rana leopardina (banded frog)	255
20.	Rana fontinalis (green frog)	10
21.	Rana halecina (shad frog)	62
22.	Bufo Americanus (common toad)	420
23.	Salamander erythronotus	6
24.	Triton	2
26.	Cyprinus aureus (gold fish)	1
27.	Salmo salar (salmon fry)	17
28.	Gasterosteus Noveboracencis (stickleback)	6
29.	Embryo of common barn fowl	4
30.	Embryo of California salmon	32
31.	Embryo of skates (Raia lævis, aculeatus)	3
32.	A large number of mollusks and microscopic organisms.	

Experiment 29.—An animalcula stage was filled with water containing numerous rotifers, keronias, and paramecium, with some vampyrellas and monads. After noting that all the animals were either actively swimming about, or that at least their cilia were acting vigorously, three-tenths of a milligramme of strychnia acetas were added. Almost simultaneously the vampyrellas in the field ceased moving, the rhythmical contractions of the vesicles in paramecium became arrested, and other species floated dead, and shrivelled or collapsed across the field. The rotifera held out longer, some of them manifesting an increased rapidity of pedicular contractions at the outset, but this may have been due to the agitation produced by the perturbation of the fluid; within thirty seconds they were quiescent and *relaxed*. Several protomonas were still swimming about at this time, but much more slowly than before, and at the end of four minutes not a single living specimen could be found. What is noteworthy in this experiment is that none of the species showed the slightest tetanic symptom. That the acid condition of the added solution might not be accused of having caused their death, I have added to a similar specimen of water an equally acid solution of glacial acetic acid; the vampyrellas especially survived a long time

in this solution, and not even the delicate keronias died before an hour or more had elapsed.

Experiment 281.—A specimen of the microscopic water crustacean, Cyclops quadricornis, was placed in the animalcula stage. As usual after transferral, the animal darted around with its characteristic abrupt dashes, then when it became quiescent, .0001 of S. was added to the water; the commotion caused by the addition of the new fluid caused it to start and dart about as normally, but at the end of twenty seconds, its dashes became shorter, as if checked half way; this gradually increased, the movements remaining as frequent, but the distance made by each movement becoming shorter and shorter, until the animal became perfectly motionless. Under the microscope, its antennæ were found stiffly extended, its caudal spines and natatory members erect, the heart was quiescent, except for a faint and almost imperceptible contraction at the end of two minutes. At the end of 2′ 40″ from the time the poisonous solution was added, the animal was relaxed, becoming opaque, a sign that it was dead.

Experiments 224, 225, 226, 227.—Four sticklebacks were placed in a large glass globe containing about one-half a gallon of sea-water, and in a well-lighted room; it was remarked that three were females, and one a male, arrayed in the crimson tints peculiar to the male stickleback at breeding time. Twelve grains (0.75) of S. were added to the water. Twenty minutes elapsed before any effect was noticed; this manifested itself by the fact that the slightest jar to the table on which the globe was standing would cause the animals to start and dart about much more rapidly, than other sticklebacks in non-strychninized water placed on the same table. Twenty-five minutes after administration, their movements became more jerking in character, and five minutes later, the females began to attack each other fiercely, and continued doing so repeatedly for a quarter of an hour. Previous to and during this stage the pectoral fins of all four individuals were moving with nearly twice the rapidity of the normal rate. This movement was clearly a respiratory one, and had for its purpose the increase in rapidity of the water current flowing past the gills. It rose and sank parallel with the functionally associated oral movements, and the animals were not propelled through the water by these fin movements; the caudal fins were motionless, or nearly so.

Seventy minutes from the time of administration, two of the females were seen lying at the bottom of the globe, their ventral and dorsal spines *permanently* erect, and so continuing until death. At intervals of five minutes the other two fish passed into the same state, the male last, and without losing his color. The rigidity of this erection, and of the entire muscular system, was so great that the previously agile and excitable fish could be seized by one of the dorsal spines, without making any attempt at escaping, and lifted out; they could be held out by the tail, as stiff as rods, and could be laid on the table without making any, even the slightest, struggle. While in the water, the only vital manifestations retained, were the color and the movements of the mouth, which seemed to be drawn into extreme extension at times. The previously increased pectoral fin movements were now abolished, the fins being in extreme erection.

At this stage, one of the females, whose oral movements had ceased, was opened, the viscera were found pale, and the heart *empty*, *contracted*, and motionless. On returning the animal to the water, its oral motions *returned*, and continued faintly and at long intervals for four minutes after, the heart remaining as before. The moment of dying was marked by a gradual and general paling of the natural tints of the body, especially of the sclerotic zone. Death took place in the four animals as follows, from the time of administration:

1. Female, opened as stated, 1 hour, 42 minutes.
2. Female, frequently disturbed, 1 hour, 47 minutes.
3. Female, undisturbed, 1 hour, 55 minutes.
4. Male, 2 hours, 6 minutes.

The significance of this experiment lies in the fact, that one complicating factor, present in higher animals, could be here, at least partially excluded. In air-breathers the initial spasms affecting the respiratory muscles, in conjunction with the entire motor apparatus, cause a partial asphyxia, which as I shall show, involves many consequences not primarily attributable to the strychnia.

Here, however, we had no asphyxia. All cavities of the heart were found empty, and the injection of the gills was normal in quantity and color. This immunity is referable to the fact that on account of the incompressible walls of the gill cavity, muscular spasm cannot affect the latter by pressure. The fish passed into their final tonic spasm before even a suspicion of asphyxia could be justified.* It might appear perhaps that the increased (respiratory) movements of the mouth and pectoral fins signified a respiratory need, but as the same movements are found equally increased in non-strychninized, *excited* sticklebacks, and as further in the strychninized specimens, increased pugnacity and general excitability co-existed at that stage, I look upon it as a psychical symptom. The salient feature in the tetanus of these animals is, that it was *tonic* throughout, not being interrupted by clonic spasms at any time.

Experiments 48 and 122.—A young alligator thirteen inches in length had 0.0075 S. injected into his peritoneal cavity. In four minutes he became more restless, and struck around with his tail; his respiratory movements became more excursive, and at 4′ 30″, his head was violently drawn back, while a slight extensor wave ran down the vertebral column. From this the alligator recovered by a visible effort, and in subsequent spasms, this struggle between the effects of the poison and the efforts of the will, could be observed—in this respect presenting a considerable contrast to the frog, who submits readily to the tetanizing influences. At intervals of from two to four minutes, the alligator had distinct spasms like the first, and in the intervals would open his jaws widely, as if to rid himself of an incipient trismus. Trismus of an intense character was a marked feature throughout, and the pupils were *contracted.* At 16′ the animal passed into a continuous opisthotonos, to which frequent successive clonic shocks were superadded.

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*That the cessation of the fin movements might not be accused of having produced asphyxia, and thus the death of the animal, during the terminal tetanus (since upon these movements depends the continuance of the branchial current) I may state that the stickleback can be kept alive for days when the pectoral fins are amputated. This fish is perhaps the hardiest denizen of our waters, and is a fitter subject for experimentation than the delicate gold-fish, usually selected.

After the spasm had lasted eight minutes, the animal being rigid and motionless (and the pupil still moderately contracted), it was opened, while the viscera were successively exposed and manipulated, the violent tetanus continued, the jaws could be heard to grate against each other, and the limbs were extended along the sides. The viscera were found pale, the lungs moderately hyperæmic, heart beating infrequently, irregularly and checked in systole, hemispheres and oblongata injected, cord normal.

Another alligator, length 18″, was poisoned *per orem*, by 0.015 S. The first spasm took place 12′ after administration, death in 1 hr. 10′. The pupils became dilated moderately before death, the lungs were found congested, the medulla and cord hyperæmic, hemispheres moderately injected.

Experiment —*An opossum received 0.25 S. *per orem*; for eighteen minutes nothing unusual was noticed, except that an attempt to "hypnotize" the animal, (which under normal circumstances is easy,) failed. Then an occasional stiffness in gait, varied by clonic spasms of the fleshy panniculus, alternating with free intervals, occurred, until 32′ from the time of administration, when a marked opisthotonos took place, lasting, with variations in degree, but interrupted by complete relaxation, until death, which occurred twenty-two minutes later. The animal never regained its feet, for the hind legs, besides being extended, were adducted, so that the claws touched each other. At intervals of a minute violent clonic spasms, lasting from two to five minutes at a time, occurred; the end of the last clonic spasm left the animal supple and relaxed, marking its death. Autopsy: all the thoracic and abdominal viscera congested, the right side of the heart moderately filled with dark blood; on pinching the heart a few feeble contractions were provoked; brain and cord hyperæmic, a large clot in the *tela choroidea*, and over the optic lobes and trapezium, color of the effusions purplish.

Experiment 1.—A large starved cat received eight grains of acetate of strychnia (0.48) wrapped up in meat, which was sewed together. A subsequent examination showed that none of the strychnia could have remained in the mouth. The

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***Not in essay as originally presented.**

symptoms are recorded in their order, counting from the time of administration. It may be stated that the dose was given in three instalments, each wrapped up as stated, was swallowed ravenously; the administration extended over two minutes. 3′, the ears twitch at the slightest sound, or even without any appreciable cause, the pupils contract and dilate under stimulus, naturally, but there is a tendency to dilatation; 3′ 20″, horripilations; 3′ 45″, it starts, as a cat would do, in pursuit, but suddenly, as if frightened, it jumps on a chair; horripilations continue; 5′, the right paw starts from its position, involuntarily without doubt, for the cat recovers its position by a manifest will-effort; 5′ 5″, the same paw starts out again horizontally, and is agitated by a genuine *epileptiform* spasm, the rest of the body, except for the movements of the hairs, being entirely quiet. This spasm was unmistakably like those produced by localized cortical electrization, and lasted 6′, the animal recovering itself as before; 7′ 8″, respirations twenty-six per minute, and not labored; previous to administration they were eighteen; 8′, it licks its mouth and acts as if it had an unpleasant taste therein; 9′, starts as if to jump through the crack of the half-open door through which I am watching it, but a stiffening of the flexors of the hind legs prevents it from carrying this out; 11′, with a violent effort, it jumps for the desired egress, but stiffens out, and turns over completely in mid-air, falling on the ground in extreme opisthotonos. For twenty seconds, general tonic and clonic spasms of the most frightfully intense character (during which the animal split one of its molars) agitated the animal; at the end of that time its pupils were found to be extremely dilated, the animal supple, death. Autopsy: brain and cord moderately injected (venous).

Experiment 2.—Full grown cat, given fifteen grains in same manner as in preceding case. The notes are fuller; I select from them the observation that the attention of the animal for the surroundings was heightened, that the diameter of the pupils reached its maximum when the spasms were at their height, and that an *epileptiform* spasm of the right ear was noticed similar to the spasm of the fore-leg noticed in experiment 1. Death occurred in nine seconds from the commencement of the only and terminal tetanic convulsion. The autopsy made immediately after death,* revealed complete anæmia of the brain and cord, heart contracted in systole; right side moderately filled with dark blood, great veins moderately filled with lake-colored blood, lungs pale.

In these experiments very large doses were given, in order that the initial symptoms should be sufficiently well marked to become objectively noticeable, it being well known that these initial symptoms (horripilations, psychical inquietude, *et cetera*), are but imperfectly developed, or even absent when the poison is given in small doses, or in minimal doses often repeated.

In the lowest animal forms, we perceive that strychnia causes death by checking the protoplasmic movements (cilia) without causing either clonic or tonic spasms. The movements of ciliated epithelium, of white blood corpuscles, and of spermatozoa, are checked in like manner. The higher rotifera and crustacea already exhibit the tonic spasm coming on gradually and terminating life without any preliminary excitement. The fish dies in the same manner, but although he does not exhibit other than tonic spasms, he shows an acceleration of the respiratory movements and increased psychical irritability as manifested in the attacks on other fish. The caudate batrachia present the same phenomena, but an occasional tremor foreshadows the well-developed clonic spasm characteristic of the caudate amphibians. The alligator, representing the highest group of existing reptiles, already manifests the combination of well-developed clonic and tonic spasms; found with mammals, but there are no intermissions. In the opossum there are intermissions of the clonic but not of the tonic spasms, in the dog and human being complete intermissions are found. These remarks I have stated apply to cases where larger doses are given, and exclude those instances in which the first spasm was at the same time terminal and fatal as in experiments 1 and 2. But in order to exclude any source of error arising from the largeness of the dose employed, I have experimented on a similar series with minimal doses, and found that if strychnia has any influence on the protozoa, at all, it kills them without producing any previous spasms; that it kills most *crustaceans* and some mollusks in tonic spasms, that fish die in the same condition, or if they survive have no recurrence of the same, that frogs, alligators and turtles either die in a mixed tonic and clonic convulsion, or if they recover from the first attack, may have a recurrence, which is always milder than the original attack, and that the mammals with minimal lethal doses, have frequent intervals, and that the succeeding spasms are not different in intensity from the first one.

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*Since writing the foregoing I have found that in order to determine the degree of injection of the cerebral vessels, it is unwise to perform the autopsy immediately after death, as then the blood, still fluid, runs from the large veins of the membrana obturatoria and the emissaries, rendering the record valueless.

In the course of these same experiments, I have found that where clonic convulsions occur, their special character depends upon the special development of the muscular periphery in a given species. In the frog and toad the clonic spasms resemble exaggerated natatorial movements, or jumps, in the turtle the powerful retractors and protractors of the head are in continual action, the head shooting out and in of the shell, and to this are added in the box-tortoise corresponding movements of the plastron. It often happens in the latter species that the limbs being protruded during a clonic spasm, are caught and pinched by the lid closing in a tonic one.* This latter instance shows that at one and the same time, one group of muscles may be in tonic and others in clonic spasms, under the influence of this alkaloid.

There is no essential difference between the herbivorous and carnivorous species, either in regard to their vulnerability to the alkaloid, or the intensity of their motor reaction.

It is a current statement in works on experimental physiology that the frog is peculiarly susceptible to the influence of strychnia. I believe this to be a fallacy, and adduce the following experiments to exhibit it:

Experiment 6—Large *Rana fontinalis*, weight 130 grammes, 0.0075 strychnia injected hypodermically. In 18″ the movements of the nasal orifice became accelerated, and the flank movements gradually increased until the animal became tetanic, agitated by frequent clonic spasms at the end of 6′. These spasms reached their maximum in one hour, and becoming weaker and less frequent, ceased at about the ninth hour of the experiment. The animal made a complete recovery.

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*One box-tortoise after the injection, closed its shell and died thus, forty-five minutes after administration.

Experiment 41.—Common bat, received 0.005 *per orem;* within six minutes violent convulsions occurred, lasting three minutes, with two short and incomplete periods of relaxation, and terminated in death. Weight of animal 118 grammes, including skin and wings. The spasms were peculiar; such was the rapidity of the clonic movements that they could not be followed by the eye, and they resembled rather a tremor than a spasm. The same peculiarity is observed in the case of the mouse.

Here approximately the same dose proportionate to the weight of the animals, had been given in the case of the frog by the direct introduction into the parenchymatous fluids, in the mammal by the indirect path of the digestive tract, and yet the mammal died, the frog recovered. I have, in comparing the weight of different species experimented on, and accounting for individual idiosyncrasies, found the minimal lethal dose to be nearly the same in the different reptilian and amphibian classes.

The fallacy referred to has doubtless had its origin in the fact that if the frog be placed in water containing small amounts of strychnia, he will react very readily by convulsions, while other animals will not. The real reason for this vulnerability is to be sought for in the greater absorptive power of the frog's skin. Other aquatic animals (newts) having the same absorptive power have the clonic spasms ill-marked, but are nevertheless under the influence of the poison. Then again the advice is often given in hand-books on toxicology, to select only *small frogs* when desirous of testing for small quantities of the alkaloid, showing that the supposed vulnerability of the frog may have had its origin in the small size of the animals employed. Larger specimens in the same jar of strychninized water with smaller specimens, will frequently be unaffected, while the latter are in full tetanus, and a bull-frog* will even in a strong solution of strychnia remain unaffected for days, when the leopard frogs in the same fluid are dead, for the reason that the former has a thicker skin than the latter.

Another observation made was that if the extremities of an animal are placed in an unnatural position before the tetanus is established and maintained so, that the tetanic rigidity will preserve that position when the constraining apparatus is removed. For example, in the case of a bat the wings were secured by weights, one of the wings being folded, the other spread out. The weights were removed when the tetanus began, and although both wings were in combined clonic and tonic spasms, the extended wing remained extended, the folded wing remained flexed. The peculiar distortions noticed in some of the instances of chronic strychnia poisoning, were due to the confinement of the animals in narrow jars.

PROPOSITION II.

That strychnia requires, for its characteristic motor effects, a well developed central nervous system, and that therefore these effects are absent in the earlier embryos.

We have already seen that the higher the development of the nervous system, the more decided became the strychnia symptoms; since the embryo of higher animals presents us with an imperfect nervous system, let us see whether the dictum holds good here also.

Experiment 21.—The egg of a common barn-fowl of the sixth day of incubation was carefully opened with a graver, and the finely developed embryo exposed. Three drops of luke-warm egg-serum, containing 0.00015 strychnia, were slowly injected by a hypodermic syringe into the amniotic cavity. Previous to this the embryo had been moving around slowly. The heart was beating about 90 per minute; the auricles and ventricles filled well in their respective diastole: 22″, cardiac beats 70, well filled at diastole; 45′, animal quiescent, cardiac beats 42′, the interval is long, the diastole imperfect, the systole very abrupt, short and complete; 1′ 30″,

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*For a similar observation see the paper of Dr. J. J. Mason, on lead-poisoning in frogs. *Trans. Am. Neurol. Assoc.*, 1877.

diastole so incomplete that hardly enough blood enters the heart to give it color; there are from this time to 1′ 49″ only three short and hardly perceptible movements of the heart when death occurs.

Experiment 22.—The egg of a barn-fowl of the twelfth day of incubation was opened, as in the preceding experiment. In order to leave the embryo in as natural circumstances as possible, the solution of strychnia, containing 0.005 was merely dropped over the amniotic sac, and the gap in the shell closed by a cover glass. The cardiac movements cannot be observed in an embryo at this stage; and further than that the creature turned round on its axis several times, a movement common to healthy embryos at this stage: it manifested no symptoms, except that the movements became perceptibly weaker, and ceased in forty-seven minutes entirely. The embryo then became opaque, and was dead. The surfaces of the yolk and amniŏn were carefully washed, and the *liquor amnii* tested for strychnia, which, besides documenting its presence by a decided bitter taste, gave the characteristic reaction with bi-chromate of potash.

Experiment 37.—A large female rabbit was secured on the tray, and, being pregnant twelve days, the left corner of the uterus was exposed and laid over on the mesentery; one of the dilatations was then carefully opened by surface section, and the embryo, whose heart was beating 112 per minute, fully exposed. A drop of a strychnia solution, containing approximately 0.0025 of the acetate, was dropped on the amniotic opening. In 22″ the heart was beating 138; but at 1′ 15″ this had sunk to 85; the heart failed to fill at the diastole; some movements (vermicular) of the body occurred, which became gradually less frequent, and a commencing opacity of the tissues marked the death of the animal, the heart having ceased moving several times and then resumed action by a few imperfect contractions.

In none of the foregoing experiments could any hemorrhages be discovered in the area vasculosa, as marking an increased blood pressure. The only action of strychnia on the earlier embryos seems to be upon the heart, which organ, after an inconstant and brief period, during which the beats are increased in frequency, shows fewer pulsations than before. At the same time the diastole is imperfect. While an imperfect diastole in an adult animal or an advanced embryo would justify us in looking to the pneumogastric nerve as the factor, the undeveloped condition of the centres of that nerve in the medulla, during early embryonic life, forces us to seek for some other influence. Shenk, of Vienna, has shown that the embryonic heart when excised and maintained at the normal temperature in serum, will continue beating, as before, and that any portion of the organ, equivalent to one-twelfth of the whole, possesses the same power.

At this period of life the proper ganglia of the heart are not yet differentiated, and the cardiac motions must be referred to associated protoplasmic action, independent of nerve centres. Those protoplasmic powers which preside over the more passive function of the diastole are first *paralyzed* by strychnia, and then those presiding over the systole suffer. It is also observed that embryos whose circulation has ceased under the influence of strychnia, die much more rapidly than those whose circulation is arrested by excision of the heart, as marked by the early opacity of all the tissues. This shows strychnia to have a lethal influence on all protoplasm, when brought in contact therewith in sufficient quantities.

PROPOSITION III.

Excluding the influence of imperfectly oxygenized blood upon the circulation, the legitimate effect of strychnia on the circulation is to stimulate the systolic movements of the heart, to contract the arteries, increase the rapidity of the blood current and to raise the blood pressure.

The egg of a salmon, containing an embryo ready to escape from the egg-capsule, is placed in a watch-glass filled with water, and after the restlessness of the embryo has ceased, 0.0003 strychnia is added. Before this addition the cardiac pulsations varied between 18 and 24 per minute. 6″ after administration violent movements occurred, rupturing the capsule, and the animal escaped; in consequence of the excitement, doubtless, the pulsations rose to 26, but after half a minute, instead of returning to their previous rate, as under normal circumstances, they rose to 32. Systole short, quick and complete; the heart does not attain full diastole, the pectoral fins move more rapidly, so that the eye can hardly follow them.

A great advantage of this experiment lies in the complete transparency of the whole animal, and the distinctness and size of the blood corpuscles, so that the changes in the blood current can be readily traced under the microscope; in 39″, the capillaries in the tail became contracted, the movement of the aortic blood current, which previously required 6″ to pass the distance of one-fiftieth of an inch, now is so rapid as to require only one-third that time; and the same thing is observed in the segmental and branchial vessels.

1′ 22″, restlessness increases, the fish occasionally beats the water with the tail; in quiet intervals the bodily axis is seen to be curved, the cardiac movements shorter, less complete and 60 per minute, complete obliteration of terminal capillary arch of tail, movements of mouth, and operculum distinctly spasmodic; 1′ 45″, several of the veins of vitellus contain motionless blood corpuscles; the column gradually accumulates until a stasis of even the larger vitelline veins is produced; at 2′ 12″ the stasis has extended to the systemic veins, and the heart is now motionless, contracted and nearly empty; 2′ 30″, slight movements of the heart occasionally recur, although there is no circulation whatever, and the tissues of the animal are becoming opaque; the oral movements continue, and occasional motion of the body is noticed until 4′ 30″, when no further signs of life occur.

Experiment 310.—In the last experiment, an imperfect supply of oxygenated water, might be accused, although erroneously,* of having produced some of the symptoms described. To obviate a possible source of error, a larger specimen was placed in a specially arranged trough for microscopic observation, and by capillary tubing a constant stream of slightly strychninized water was kept continually running through the trough. The degree of concentration was such that the whole quantity of water in the trough at any one time was about .000000005, the entire quantity of strychnia to which the animal was subjected was 0.006. Before and during the first part of the experiment, the animal was very vivacious and it was difficult to keep a given part in field. Commencement, heart beats 36, oral movements rare, and come on only after excitement; pectoral fins in constant motion, circulation of vitelline vessels more active than in the last specimen, in capillaries of tail the rate is similar to that noticed in a frog's web, but without the local interruptions observed in the latter instance. No change occurs for 2′ 30″, when the animal becomes markedly restless and the cardiac movements rise to 64. At 5′ it is quiet again, the capillary and general circulation is at least twice as rapid as before, the capillaries are much more contracted than in a similar embryo under normal circumstances, at 7′ 45″. At 12′ the motion of the blood is occasionally checked; on examining the heart at such times it is found arrested in tetanic systole. At 22′ this systolic contraction having recurred four or five times, the capillaries are found filled with stationary blood corpuscles, the arteries are contracted, the veins distended, and after a few spasmodic oral movements, death took place in 24′ from the commencement of the experiment, in tonic spasm.

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*Stasis occurs when a non-strychninized fish dies by asphyxia, in from fifteen to twenty minutes, but the heart is not found contracted.

Neither in these nor in similar experiments could any diapedesis of blood corpuscles be observed. At the same time the blood in the arteries was arterial *throughout*. This fact is readily determined in these almost glass-like transparent creatures, by the fact that in very thin layers their arterial blood has a clear yellowish tint, while the venous has a greenish hue, pronounced enough to enable us to distinguish between the two kinds. No movements were produced in the intestinal canal.

I have also confirmed the observation of Richter, that in the case of the frog's web and bat's wing, contraction of the arterioles and capillaries is one of the constant phenomena of strychnia poisoning, in this respect being similar to the fish's tail. I have further observed that division of the nerves going to the hind leg of the frog, in which instance the tetanus of the extremity is abolished, did not entirely abolish this contraction of the vessels. This has led me to infer that the increased arterial pressure is not exclusively due to the effect of strychnine on the central nervous system, and will have to be regarded distinctly from the effects of the alkaloid on the central nervous system.

I have not been able to derive any satisfactory results from the employment of the manometer and kymographion in mammals. The customary employment of chloral hydrate and curare, to paralyze the muscular contractions, adds countless sources of error to the experiment, and where we dispense with these antidotes, the elements of asphyxia, of muscular compression of the venous conduits, and the abnormal psychical condition, render any record by these delicate instruments futile. For the latter reasons also, the observation of the circulation in the pia, through a glass plate in the trephined cranial opening, could only be utilized in a general way. It seems that the arterioles contract just precedent to the first convulsion, but during this and all subsequent convulsions, as well as in a lesser degree during the intervals, venous engorgement is constant.

Our fourth proposition is already partly involved in the results of the foregoing experiments.

PROPOSITION IV.

That some of the effects of strychnia on the vaso-motor system are independent of its influence on the central nervous system.

Experiment 11.—Small *Rana fontinalis*, secured and web fixed in field of microscope, first under a Gundlach II, latterly under a Gundlach V. Strychnia 0.01 *per orem*, to avoid the undesirable effect of a hypodermic injection (it being known that with sensitive frogs a puncture of the skin will suffice to produce capillary contraction, or even momentary stasis). At the end of one minute the capillaries and arterioles gradually and generally contracted; at 1′ 50″, a tonic spasm, during which all the arterioles contract almost to obliteration, while the veins become fuller; 2′ 10″, several clonic spasms, during which the circulation becomes re-established; 2′ 45″, a second tonic spasm, the arterioles only in medium contraction, venous stasis for twelve seconds; 3′ 30″, arterioles considerably contracted, and this contraction increases during the next two minutes, while the animal is free from spasm; 8′, the nerves of the left posterior extremity are isolated and divided high up; during the progress of the operation the animal passes into tonic spasm, preceded by a series of clonic convulsions; after division the left hind leg was supple, while the rest of the frog was in tetanus; 12′ 30″, arterioles still contracted, vascular current accelerated, no peripheral layer of motionless corpuscles, nor diapedesis; 1 hr. 21′, arteries still contracted; during severe clonic spasms there is temporary and evanescent engorgement of veins; 1 hr. 50′, relaxation of spasm, arteries less contracted, but still not of normal calibre; 2 hrs. 2′, the arterioles become gradually contracted again, and with the almost total obliteration of some vascular areas, the frog passes into tetanus; observation closed.

Experiment 12.—In a young *Rana leopardina* the right hind leg is severed, the artery and deep vein alone being preserved; after the circulation in the web had returned to an approximately normal condition, 0.015 strychnia was injected into the limb; in 12′, complete and progressive contraction of the arterioles and capillaries; in 30′ tetanus.

Experiment 14.—In a small frog of the same species, secured in like manner, a similar division is made, but in addition the vein is divided; 0.015 strychnia injected into separated limb. The circulation in the web is much less interrupted under these circumstances, than one would suppose *a priori*, and a visible effect is produced by the alkaloid; in 19′, a notable contraction of the net-work; no tetanus.

Experiment 13.—Another frog of the same species, secured in like manner, has the spinal cord destroyed by passage of a sound, leaving the medulla and that part of the cord above the origin of the great brachial nerve intact. The vagi and sympathetic cords divided. Strychnia being administered (dose uncertain) the same contraction of the vessels in the web is observed. It seemed to be produced much more slowly than in an uninjured specimen, but the effect was marked and continued for five hours, no venous stasis occurred, and the contractions continued until death. Peripheral irritation (of the web) increased the contraction. Tetanus existed only in the head, and hyoid regions. Experiments 15, 16, 17, repetitions with same result.

Experiment 18.—Large *Rana leopardina*, cord destroyed as in Experiment 13; the animal previously received 0.05 subcutaneously. On placing it on the edge of the table, with the hind legs dependent, no œdema occurred in these parts. In non-strychninized frogs such œdema is almost a constant phenomenon under these circumstances.

From these experiments but one conclusion can be drawn: that the vaso-motor influence of strychnia is in part at least independent of the central nervous system, for the contraction of the vessels persists after the nerves are divided (Experiments 11, 12), and after destruction of the greater part of the cord (Experiment 15). The engorgement of the veins is also shown to be a mechanical phenomenon, for it reached its highest point while the animal was in tetanus, and was absent naturally when the vein was divided, as well as where there was no tetanus of the trunk muscles. The œdema following the vaso-motor paresis induced by destruction of the cord is therefore absent in strychnia poisoning. In this independency of strychnia with regard to its vaso-motor influence, it is analogous to nitrite of amyl, which, according to Huizinga, also may act locally on the blood-vessels.

PROPOSITION V.

That the peripheral nerves take no active part in the production of the typical strychnia symptoms, and that no anatomical changes occur in their structure.

Experiment 3.—The crural and sciatic nerves of a large toad were divided on one side in the altitude of the coxo-femoral joint, without loss of blood. The leg was completely paralyzed. Strychnia 0.1 injected under the skin; within 1′ full opisthotonos and clonic spasms of trunk, head, both anterior, and right hind leg. The divided member (left hind leg) remained quiescent throughout; the animal died in twenty-two minutes.

Experiment 10.—Large *Bufo*, 0.006 subcutaneously; usual prodromata, complete tetanus in 62″, during the progress of which, the nerves of the left hind leg were divided. The division was completed 6′ from the time the first tetanic spasm had manifested itself, and the limb which till now had been rigid and convulsed like the rest of the body, became as relaxed and quiescent as in Experiment 3, for four minutes. At the end of that time it participated slightly in a clonic spasm; on reopening the wound, I found a delicate branch of the plexus intact; on its division no further symptoms occurred in that extremity, the animal dying in four hours.

Sixteen other toads, in whom various nerves had been divided in the anterior and posterior extremities, exhibited correspondingly absence of tetanus in the muscles supplied by the divided nerves. The same was observed in mammals. I found in several of these instances that the discrepancy between authors with regard to the paralysis or non-paralysis of the motor nerves, can be easily explained. The reaction of the sciatic nerve was unaltered in those animals which, either on account of their size, or the smallness of the dose received, suffered only a moderately intense tetanus, and for a short time; but the longer the tetanus had lasted, the greater its intensity, the more the reaction became diminished. I had in the earlier experiments given large doses of the alkaloid to toads, and found them relaxed and apparently dead four or six hours later. In making autopsies of such animals, I found the heart still beating, and from this was led to watch other apparently dead toads for some further time before throwing them away, and was frequently surprised to find an animal previously supple, and of a cadaver-like softness, return to life (especially after a cool evening) in from six to twelve hours. In three instances I found a *repetition of the tetanus*, occurring on recovery; and with or without tetanus the recovery was never permanent, for the animals died in an asthenic state.

One toad was tested as to his reaction, while in the condition of apparent death, and this was found *nul;* when he again showed symptoms of animation, it was obtained.

In a large frog that had been in tetanus thirty-seven days, the nerves of the left hind leg were divided, the tetanus continued in the other leg as well as in the trunk, but the operated limb was quiescent, and on testing the exposed nerves of both sides four hours afterwards a difference of four centimetres found in favor of the left (operated) limb.

From these facts I am led to look upon the diminished reaction, not as the result of a specific paralysis produced by strychnia, but as analogous to the diminished reaction which follows *any over-exertion of the voluntary muscles.* That strychnia exercises no special influence on the nerves in this direction is shown by the fact, that where the nerves are divided, and where as the sequel will show, it can be chemically traced in the nerves of the operated limb, no difference from the reaction of the separated nerves of a non-strychninized animal can be observed, while the further the tetanus proceeds in the opposite member, the less pronounced the reaction.

Experiment 270.—Medium-sized *Rana fontinalis;* chronic tetanus had lasted seventeen days. The nerves of left hind leg divided as in Experiment 3; immediately the tetanus ceased in that limb, while it continued until the death of the animal (which took place two days later), in the rest of the body. The sciatic nerve of the unoperated limb was examined microscopically, and not the slightest indication of a change observed; its sheath was hyperæmic.

I have after numerous examinations made on the nerves of animals killed suddenly by large doses, as well as killed by the long-continued use of minimal doses, arrived at the conclusion, that strychnia produces neither primary nor secondary changes in the tissue of the peripheral nerves.

Having proved that division of the nerves instantly abolished strychnia tetanus, it behooves us to show whether the continuity of the nerves is sufficient to maintain the limb in tetanus, if the circulation is interfered with.

Experiment 38.—A large toad is secured on the operating table, and the integument of the right hind leg being divided by an incision encircling the limb, the crural and sciatic nerves are exposed and isolated. The blood-vessel accompanying the sciatic nerve is torn through purposely, and then the entire extremity is amputated, with the exception of the previously isolated nerves, which are kept moistened by serum. Hypodermic injection of strychnia 0.001. In 2′ violent clonic spasms of the whole body, *synchronous* spasms of leg and foot of amputated limb. The only difference between the right and the left leg was that the spasms of the femoral muscles were limited to contractions of the divided bellies, and produced no movements of the limb as a whole. The death of the animal occurred the next day, eighteen hours after operation; and while the tetanus continued in the body as a whole, to the time of death, it ceased four hours earlier in the amputated limb, its nerves having softened, and the tissues decomposed.

Experiments 39, 40, 44, and 42 confirmatory. These experiments signally prove that the muscular tetanizing influence is conveyed from the central nervous system to the muscles by way of the peripheral nerves, that it is not modified by the nerves, that the latter play merely the part of passive conducting mechanisms, and that as such, if the central nervous system is intact, they alone are concerned in conveying the tetanizing influence.

Experiment 43.—The left hind leg of a *Rana leopardina* is separated as in Experiment 38, the crural and sciatic nerves being left intact, the limb is then immersed in a saturated strychnia solution. Left therein for twelve hours; *no result.*

Experiment 47.—Repetition; same failure; the proximal extremity of the amputated limb was then permitted to touch the level of the fluid; in 16′ general tetanus; the mutilated limb which, suspended in a saturated solution for six hours, failed to show any spasms, now had them well marked.

Experiment 228.—Rabbit: left femoral and sciatic arteries ligated, extremity amputated, excepting the great nerve trunks, which were previously isolated (no chloroform employed); 0.006 injected into neck; animal in extreme tetanus in 18″; mutilated extremity agitated by clonic spasms, until death, 2 hrs. 20′. Care was taken to keep the limb warm, and the nerves moistened with serum. It was observed that there was a symmetry of the hind legs as to the time, rhythm and duration of the spasms. On testing for strychnia, no evidences were obtained from the distal part of the left sciatic nerve; faint traces were obtained from the right, and from the left above the line of amputation, which I did not consider very decisive; I therefore selected a larger animal and gave maximal doses of strychnia.

Experiment 229.—Large mongrel dog; 25 grains of strychnia acetas *per orem*,* 12 grains per rectum in solution. The left hind leg was then separated as in the last experiment, and as soon as the first symptoms of strychnia poisoning (labored respiration, horripilations,) showed themselves, which was 32′ after administration, one gramme more was injected in solution in three different parts of the body. During the injection the animal passed into a violent general tetanus which continued without remission 11′, when relaxation and death took place. The entire length of the sciatic and the greater part of the crural nerves of the right side were placed in one test tube, the same nerves of the left side below the line of amputation in another. Portions of other divisions of the nervous system were also preserved, the results of their examination will be referred to in another place. The contents of the first two test tubes, the one containing the left nerves designated as A, the other as B, were digested with a mixture of two parts of muriatic acid to ten of water for two days, until they were completely fluid, the emulsion was filtered, the part remaining on the filter being redigested and refiltered, and treated with commercial alcohol as long as anything more would dissolve. The residue was repeatedly washed with water and filtered. The resulting fluid was evaporated to dryness in a water bath, and this residue in turn treated with alcohol, for three days, filtered and evaporated, again dissolved in water and again filtered. Now liquor ammoniæ was added in excess, and the whole shaken up in a flask with chloroform. The latter having subsided was then drawn off with a pipette, and rapidly evaporated on a water bath; the dry residue then moistened with sulphuric acid (monohydrous) and exposed to the water bath again. The charred matter was finally dissolved in water, again treated with an excess of ammonia and chloroform, this procedure being repeated thrice, until the sulphuric acid ceased to char the evaporated residue, when it was suspended in chloroform; a drop of this solution after partial condensation by evaporation was dropped on the bottom of a warm porcelain capsule; as each drop evaporated another was added. As soon as the capsule was cooled off, the residual coating was moistened with strong sulphuric acid, a minute crystal of bichromate of potash being laid in the centre. In specimen A no result followed, in B the spot turned successively blue, violet, a beautiful crimson, red and green; the latter color remaining permanent.

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* Wrapped up in meat.

Thus the presence of strychnia in the muscles and nerves themselves is shown to be unessential to the production of tetanus.

PROPOSITION VI.

That strychnia increases the sensibility of the peripheral organs of sense, but that it is an error to therefore designate the convulsions of strychnia as the sole result of an increased reflex excitability of the cord.

Regarding the first part of the proposition there are no differences of opinion among observers. Strychnia in therapeutical doses has a marked effect upon the peripheral sense apparatus, which effect is even more patent in pathological cases. We see this very clearly in the case of amaurosis, especially when due to toxic influences (nicotin poisoning); a recent writer has indeed found that by brushing a solution of strychnia on the regio olfactoria of healthy as well as of anosmic individuals, the acuteness of the sense of smell could be increased. If this observer's (Möller) results are confirmed* they clearly prove that the heightened sensibility is in part at least peripheral, whatever share the heightened functional activity of the nervous centres may have.

If the old dictum, that the strychnia tetanus is solely adducible to an increased reflex excitability were correct, then the occurrence and intensity of the spasms would constantly depend upon the occurrence and intensity of the peripheral irritation. That is far from being the case. One frequently observes a frog passing into tetanus, on irritation, who recovers, and crawls away or sits still, in spite of frequent repetitions of that irritation. When left to himself, and while everything is quiet, he suddenly develops an exquisite tetanus. In a large goat, poisoned with a large dose of crystalline strychnia, and where on account of the slight solubility of the alkaloid in the gastric juice, the symptoms were delayed a long time, it was observed that the prodromal horripilations came on without any regard to the occurrence of disturbance. But this question can be submitted to crucial test.

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* I confess that it is very difficult to control such a difficult operation as painting the regio olfactoria with such a solution, properly.

Experiment 282.—Large bull-frog; the brain and spinal cord exposed for their entire length; the posterior roots of all the spinal nerves, the auditory trigeminus (which, in the frog, includes the glosso-pharyngeal) and optic nerves divided. All sensory impressions, except those of smell and the visual sensations were, therefore, excluded. To remove the former, the olfactory lobe was separated from the cerebrum. Fifteen minutes after the operation, 0.0015 strychnia injected into dorsal wound. Within one minute complete opisthotonos, preceded by a brief clonic spasm. The tetanus presented the same picture as that of an uninjured frog, except that jarring the table failed to bring on the spasm, although direct irritation of the cord and medulla did so. The spasms, however, became more anenergetic towards the end than in an unmutilated frog.

When the animal was picked up and thrown down violently, it responded like an uninjured frog, by a tetanic spasm; but here, probably, the direct influence upon the nervous centres by concussion was the causal factor: for the skin could be pinched, the toes cut away singly, the leg amputated, and the eye pinched, without any such result.

Experiment 296.—Kitten twelve days old; division of posterior roots of all the dorsal and cervical nerves; then division of cord at atlo-occipital articulation, and also below middle dorsal region. Where the roots were left undivided and a corresponding division of the cord was made in another kitten of the same litter, it had been previously ascertained that perfect tetanus ensued in the head, trunk and anterior extremities when strychnia was administered. In the present instance 0.01 strychnia injected into dorsal wound; in 40″ trismus and extension of head; at 3′ 45″, a sudden tetanus of the trunk and anterior extremities, passing into clonic spasms, with which the animal died at 6′.

Here all sensory influences on that segment of the cord from which the nerves of the trunk and anterior extremity take their origin, were abolished, and yet we obtained the typical strychnia spasms. The delay in the response of the cord noticed in the last experiment will be discussed elsewhere. The experiments of Freusberg, Mayer and Möller have paved the way for regarding strychnia as a primary irritant of the grey matter, a view which my experiments fully confirm.

That peripheral irritation increases and maintains the tetanus and spasms, remains, nevertheless, a fact; and this has been recorded by the earliest experimenters. What, therefore, the originality in the recent suggestions of a French writer consists in — who recommends darkness and quiet as important adjuvants in the treatment of strychnia poisoning — it is difficult to see. The older physiologists have long ago noticed that recovery is more likely, under these circumstances, and almost every therapeutical hand-book embodies these suggestions. I have employed darkness and quiet as most important aids in keeping frogs alive for weeks, under the influence of the alkaloid. [See chronic strychnia poisoning.]

PROPOSITION VII.

That strychnia acts upon the entire grey matter of the central nervous system; that the characteristic tetanus is due to the effect on the axial tract (central tubular grey matter), whose upper extremity (pons, medulla and cervical cord) is more concerned in the production of the spasms than the lower (lower cervical, dorsal and lumbar cord).

The question as to whether strychnia is to be considered as exercising a *cerebral* or a *spinal* tetanizing influence, is the most disputed one of this subject under discussion at the present time. Two of the most recent experimenters flatly contradict each other on this point — Mayer claiming that the spinal cord *per se* could not produce spasms, under the influence of strychnia; Freusberg, on the other hand, asserting that it is the part chiefly concerned. We shall find that both are wrong, and that the truth lies between.

Experiment 50.—Large toad; lumbar cord divided crudely as only the left hind leg hung passively, it was to be presumed, and the autopsy confirmed this, that only a part of the cord and *cauda* was divided. Gave 0.005 with Pravaz's syringe into peritoneal cavity; in 1′ accelerated flank movement, in 4′ clonic and tonic spasms of whole body, except left hind leg.

Experiment 54.—Toad; division of cord higher up, above origin of crural nerves; 0.005 strychnia; perfect tetanus of head, trunk and anterior extremities; posterior extremities relaxed, and quiescent until death.

Experiment 55.—Toad; division of cord, a millimetre below lowest brachial nerve; absence of tetanus in hind legs; tetanus of trunk less perfect than in Experiment 54.

Experiment 56.—Large *Rana leopardina;* cord divided immediately above the point where the greater brachial trunk is given off; the animal was allowed twenty-four hours to recover. As frequently has been observed, several hours after operation, *spontaneous* tetanus (rigidity) occurred in the hind and fore legs, from which the animal recovered. Twenty-four hours after operation, 0.005 strychnia subcutaneously. 3,′ pupils dilated, eyes protrude, tetanus in head (hyoid, extensor capitis, ocular and mandibular muscles), with "lifting" synchronous movements of fore legs. During this period of perfect head and imperfect fore leg tetanus, the movements described by Pflueger would occur, as in non-strychninized frogs, when the board on which the animal sat was tilted; that is, the hind legs would recover themselves when there was danger of falling. 2 hrs. 40′ later, a second dose of strychnia, 0.0025, was given; this was added to the water in the jar, to which the animal was transferred. The following morning the head and fore legs were still in the same tetanus as the day before; in the course of the day, occasionally, similar spasms could be provoked in the hind legs on irritation; these were not synchronous with the head spasm, and consisted of an imperfect extensor spasm, produced by violent irritation, such as throwing a book on the table. During the afternoon, the head tetanus continued unabated — frog still in strychninized water — but no spasms whatever in posterior segment of body; the fore leg tetanus became weaker and weaker, and was finally abolished. The third day, the head spasm was very marked, no other part of the body affected. In the afternoon, animal apparently dead; on opening body, heart found beating, regular and full, at the rate of eighteen beats per minute.

The disappearance of the fore leg spasm after it had once become established, points to a disorganization of the lowest part of the anterior segment of the cord, produced by the operation and resulting hemorrhage; it has, therefore, no essential bearing.

Experiment 160.—Large toad; division through anterior part of optic lobes; instant ataxic paresis of all members; occasionally, chorea-like movements. Injection of 0.005 strychnia subcutaneously; tetanus perfect, as in uninjured animals, with the sole difference that reflex tetanus would not occur on exposing the animal to a bright light.

Experiment 117.—Toad; division just below cerebellar valvule; after operation, tonic flexion of trunk and extremities, these being folded inwards. On injecting 0.005 strychnia, violent reflex struggles to free the extremity injected. When this animal jumped, previous to being put under the toxic influence, it regularly rolled over on its back; during the inception of the tetanus it rolled over in like manner. Tetanus general but not typical; in one hour and twenty minutes, death.

Experiment 114.—Incomplete destruction of medulla; usual strychnia tetanus.

Experiment 115.—Toad. Complete separation of medulla from cord; a second division below cerebellum; tongue protruded during operation; apparent death. Tetanus as usual, except that the tongue remained protruded.

Experiment 116.—Two transverse incisions in nervous axis of toad, the anterior separating the cerebellum from the optic lobes; the posterior one-eighth of a millimetre below calamus scriptorius. There was complete retraction of left eyeball, and contraction of left pupil; protrusion of right eye and dilatation of right pupil, as a result of operation. Strychnia 0.005 subcutaneously; tetanus of tympanic, hyoid and cephalic muscles within 2′, followed in 4′ by general tetanus of trunk and extremities. At no time were there any spasms of ocular muscles; these remained as before administration.

Experiment 124.—Division just above first cervical pair in toad. Strychnia 0.0025; well-marked tetanus of head and upper part of trunk, none of body or extremities.

Experiment 201.—Same division in a *Rana leopardina.* Tetanus general.

Experiment 202.—Same division in another *Rana leopardina.* Strychnia 0.0025; well-marked tetanus of head within 1′; for eight minutes the members were perfectly quiescent; at the end of that time the extremities shot out in ideal tetanus, and remained so for twenty-eight minutes, when relaxation of these parts took place, although the head was still rigidly tetanized. During the following half hour, the head spasms became clonic, the shocks becoming gradually more marked and frequent; and at the end of this period, the extremities again shot out, and were agitated by clonic spasms. When these ceased it was easy to renew them by appropriate irritation. From this time on, the spasms of the extremities became less perfect and rarer, while those of the head continued unabated until death—four hours from the time of administration.

Experiment 203.—Same operation in same species. The animal was frequently pinched, thrown on the floor and otherwise disturbed after the poisonous agent had been administered. The extremities showed no tetanus until seven minutes from the time the head had been affected.

Experiment 204.—*Nannemys guttata* (small yellow spotted turtle). Division of cord between roots of second and third cervical nerves; strychnia 0.01; tetanus of head and hyoid muscles, none of retractor capitis or extremities.

Experiment 205.—*Chrysemys picta* (painted turtle). Division through calamus scriptorius; strychnia 0.015; complete and general tetanus.

Experiment 319.—*Rana leopardina,* which had been in strychnia tetanus for eighteen days. Cord divided through region of first brachial nerve; instant cessation of tetanus in extremities, but continuance of tremors* in same.

*** These tremors are not essentially strychnia symptoms. See sequel.**

The evidence of these experiments is, on first sight, somewhat confusing. This much is certain, however, that the lower down the cord is divided, the more certain are we of rendering it impossible for strychnia to tetanize the muscles deriving their nerves from the lower segment. Division in batrachians of the dorsal portion of the cord, will prevent tetanus in the hind legs (Experiments 50, 54, 55); in the majority of animals division, as in Experiment 56, will check tetanus in all extremities. It further appears that division above the origin of the brachial nerves, even when it does not prevent tetanus, will delay the spasms for an appreciable period of time, varying from three to fifteen minutes (Experiments 201, 202, 203). The delay is manifested by the relatively earlier occurrence of the head tetanus; and that it is not due to lack of reflex irritation, a comparison of experiments 202 and 203 will demonstrate.

Division above or in the latitude of the calamus scriptorius, exercises no influence on the general spasms.

Altogether, these experiments show that the further removed any portion of the cord is from the medulla oblongata, the less likely is it to react on strychnia by itself, and that in regard to strychnia, as in some other respects, the medulla deserves the name of a veritable convulsive centre.

All animals are not alike in this respect. In tritons, tadpoles, salamanders and fish, section of the dorsal cord will not check tetanus in the muscles supplied by the part behind the line of section. It is singular that a similar result should be obtained in the case of the newly-born of higher animals.

Experiments 146–150, inclusive.—Five kittens of one litter, thirty-six hours old, were each injected hypodermically with 0.05 strychnia. In three, the section of the cord was made before convulsions appeared; in two, after.

Experiment 146.—Section through lower cervical cord, before convulsions had appeared. Subsequent tetanus general; pupils *contracted;* death in 6.′.

Experiment 147.—Section through lower dorsal cord before tetanus. Subsequent tetanus well-marked, except in posterior extremities, where it was feeble; but the tail was in the typical erection.

Experiment 148.—Section one millimetre below obex. Subsequent tetanus general; pupils dilated.

Experiment 149.—Section through middle dorsal cord; after tetanus became established, no relaxation of posterior extremities; death in 12′.

Experiment 150.—Section through lower dorsal portion of cord, after established tetanus. Tremors of hind legs follow the section, which gradually abate, leaving these parts in rigid tetanus; this in turn passes away, but is brought on again by pinching the tail. This again abates, and death takes place in 19′.

Here, while section of the cervical and upper dorsal cord did not have the effect of checking the spasms, which effect was noticed in adult amphibians and reptiles, and which we shall also find in adult mammals, still we find that division in the lower dorsal region diminished, if it did not check the tetanus in the hind legs, thus confirming the truth of our general proposition.

In older animals the effect of such section is much more pronounced.

Experiments 172–176, inclusive.—Five kittens of the same litter, twelve days old, treated as the last set, three being strychninized after, two being strychninized before section of cord, in various attitudes. Of the former group, one (Experiment 174, corresponding to 148 of last series) died before any observations were made.

Experiment 172.—Division of lower cervical cord before tetanus. Subsequent tetanus general, but trismus preceded the general tetanus by 1′ 15″; death in 3′.

Experiment 173.—Division of lower dorsal portion of cord, before administration. On administration, no tetanus of posterior segment of body; at 5′ 30″ a twitch of the tail occurred, which was of momentary duration, and was not repeated; death in 29′.

Experiment 175.—Division of middle dorsal cord, during opisthotonos. At the moment of division a fibrillary tremor occurred in the hind legs, and the tail became relaxed. The whole animal then passed out of spasm; but within 45″ it became convulsed in head, fore feet, and trunk; 20″ later this extended to posterior segment of body. On irritating the posterior extremities, the spasms became intensified. Death in 18′.

Experiment 176.—Section of junction of dorsal with lumbar cord, in altitude of last dorsal nerve, during opisthotonos. Cessation of tetanus in hind legs and tail; death in 20′.

Experiment 177.—Half-grown pup. Division of cord between atlas and axis; artificial respiration; strychnia 0.05, subcutaneously. Tetanus of head-muscles; trismus in 1′ 30″; in 4′ an imperfect clonic agitation of body, which ceased after having lasted five seconds, and recurred, but with still more diminished intensity, three minutes later. During all this time, the trismus and oculo-motor spasms were extreme. At the time of death only the head was affected (12′).

Experiment 152.—Full-grown terrier. Chloroformed; cord divided at seventh cervical vertebra. Before recovering from anæsthetic, 0.075 was injected under skin, and within one minute the head was in tetanus, and the fore legs were in a fibrillary spasm, which progressively merged into clonic convulsions. Death in eighteen minutes, no tonic or clonic spasms having occurred in posterior extremities.

Experiment 153.—Full-grown mongrel cur. Cord divided between second and third cervical vertebra. The operation was performed hastily, to give the animal the best chances of recovery, and was permitted to recover from the effects of the chloroform. Strychnia 0.06, subcutaneously. In 1′ head affected with the most extreme tetanus, the teeth grating on each other. Artificial respiration was maintained; and the pupils were observed to be moderately contracted. For nine minutes not the slightest movement occurred in the trunk and extremities, although peripheral irritation was not wanting (respiratory manipulations). Suddenly, and without premonitory symptoms, a violent tetanic spasm agitated the extremities, trunk and tail, lasting 2′ 30″, and giving way to complete relaxation; during this period of relaxation, the head continued in spasm, the jaws being firmly set, the ears and nostrils twitching, the extensors of the head being in contraction. *As long as artificial respiration could be maintained, the pupils were contracted;* as soon as it was suspended, they became dilated. *During the suspension of the artificial respiration, no spasms occurred in the trunk, nor were those of the head intensified.* After a quiet interval of five minutes, the tetanic spasms became permanently established, and were synchronous with those of the head. Death, 36′ after administration.

On the autopsy (given fully under the head of "pathology") it was found that the cord had not been completely divided. The anterior fissure of the cord had not been reached, and part of the right anterior and the whole left anterior, with part of the left lateral columns, were intact. Therefore the passage of the tetanizing influence of the medulla oblongata, although at first impeded, was, when once established, permanent. As a collateral result we observe that when the disturbing element of asphyxia is removed, that contraction and not dilatation of the pupil results.

Experiment 210.—Half grown dog, cord divided with the exception of the anterior columns, in the same altitude as in the preceding experiment. Interval between first head and first trunk spasm (which came on as abruptly as in 210), a little over four minutes. General persistent tetanus after twelve minutes; completed division of the cord at 14′, whereupon the spasms continued in the head as heretofore, those in the body instantly ceased; at 17′ a weak spasm of a clonic character recurred, and ceased in ten seconds, but the head spasm continued until death: 18′.

Experiment 213.—Terrier; cord divided as incompletely as in 210 and 153; interval between first head and first trunk spasm, 6′. Completion of section at 9′, cessation of trunk spasms as before. Thirty-three minutes later, clonic spasms lasting 11′, began in the hind limbs spontaneously, gradually involving the trunk and fore legs, until the trunk was in complete opisthotonos; relaxation followed lasting 2′; second tetanus (since completed division) partially clonic, lasted 3′ 30″, interval 6′; third tetanus, less energetic, interval 11′; fourth spasm momentary; no further spasms of trunk or extremities until death (2 hrs. 10′ after administration). During all this time head tetanus continued with *undiminished* intensity. Apparent death 2 hrs. 5′, after administration; on opening thorax, heart found beating slowly, imperfectly and infrequently.

Experiment 214.—Terrier; complete section of cord in same place, no chloroform used, strychnia 0.10 hypodermically; first head spasm 3′ after pupils contracted, first body spasm 22′ later, gradually weakening in energy as in 213. Death in 1 hr. 15′, head spasms energetic to the end. Rigor mortis came on immediately after death in head, not established in trunk and limbs for three hours.

These experiments show that even high division of the cord will delay the occurrence of strychnia tetanus in the trunk and extremities for from ten to thirty minutes, especially if the dose has been moderate. It is also noteworthy that the tetanus of the cord is less energetic, and ceases sooner, than that of the medulla oblongata. It appears that the lower down the cord is divided, the earlier is its "strychnia excitability" exhausted. That the maintenance of long-continued convulsions depends upon the intactness of the communications with the medulla oblongata, is proven by Experiments 210 and 213, where, while there was some delay of trunk spasms after partial division, these spasms were perfect and energetic when once established, but when the division was completed, these lost in intensity and frequency. This seems to prove that a certain accumulation of irritations in the medulla is necessary before the tetanizing influence can pass the narrow bridge of white substance left in the former instance, and that when this bridge is destroyed, the removal of these influences is manifested in the weaker character of the spasms of the completely separated lower cord-segment. It also points to the anterior columns, as the conductors (in part, at least) of the tetanizing influence. Several experiments which I will not take the space to record, prove that division of the posterior white columns and the posterior grey cornua, fails to check the convulsions in the slightest; to some extent this strengthens the view that increased reflex irritability is not as important a factor in the production of strychnia tetanus as is often supposed.

I do not think that there is any source of error in these experiments; that, for example, the division of the cord itself, or of its vessels, interfered with the legitimate effects of strychnia. If a suspension of the blood supply were the cause of the suspension of the tetanus, why should the latter be most marked in case the lumbar cord is divided, and least marked where the upper cervical cord is cut? In the latter instance the blood supply is interfered with most; in the former, on account of the numerous branches from the lumbar and intercostal arteries, not at all (practically). As wrong would it be to state that spinal shock had delayed the usual strychnia manifestations: for in several experiments we have permitted the animal to recover from this shock, and yet had the same result. Then in the beautiful and crucial experiment, where the cord of a frog in chronic strychnia tetanus was divided, we had instantaneous cessation of the tetanus, but a continuance of the tremors, due to an artificially induced pathological condition, thus clearly and amply demonstrating that the shock of a section does not affect the convulsibility of the cord *per se*. I feel rather inclined to seek for a source of error in the inferences of those, who not only do not content themselves with stating that the strychnia tetanus is essentially spinal, but go so far as to claim that division of the cord increases its intensity. It is true that occasionally a convulsion occurs after division, which is, if not more violent, at least as violent as the severest strychnia spasm, being both maximally clonic and tonic combined; but this very spasm occurs in many animals, who, without receiving any strychnia, have the cord divided; it is not a strychnia convulsion at all!

Our general conclusion with regard to warm-blooded animals is that strychnia affects the entire tract of grey matter, but that, in adults, as a rule, its influence on the cortex and on smaller segments of the cord is unnoticeable, if given in moderately poisonous doses. That the older the animal, the more the strychnia-excitability of the cord is diminished, until, in the adult, it may become almost zero in the dorso-lumbar region. The maximum of excitability is confined to a region bounded by the anterior border of the pons in front and the level of the second cervical nerve root behind. In this respect, there is no noticeable difference between the mammalia and the acaudate batrachia. When very large doses are given, premonitory spasms (monospasm, Experiment 1) are sometimes observed; these may be cortical, the horripilations and panniculus spasms may be referred to the hemispheres likewise, since they probably have a psychical motive.

PROPOSITION VIII.

That convulsions, although characteristic of, are not essential factors of, strychnia poisoning; and that strychnia can produce death, without the complications of nervous exhaustion, asphyxia, or cardiac paralysis.

I have already registered several experiments in which death occurred so rapidly in mammals, that there was not time enough for the development of asphyxia, as in the case of the bat, an animal which will survive many minutes after ligation of the trachea, and dies in a few seconds under the influence of strychnia. We have also seen that in lower forms of life, spermatozoa, leucocytes, infusoria, *et cetera*, death occurred without any vital manifestations. It remains for us to see how far this holds good for the mammalia.

Experiment 80.—Half-grown cat; jugular vein exposed, secured above and below an incision, through which 0.4 strychniæ murias is injected. Ligatures rapidly tightened, animal loosened, jumps over and falls on its back, in a violent momentary opisthotonos; death in 47″ from time of injection. The pupils were in medium contraction, the tongue caught between the teeth, heart beating feebly and tremulously for one minute and a half longer.

Experiment 81.—Puppy; 0.2 strychniæ murias injected into external jugular vein; almost instantaneous twitches of entire body; apparent death in 1′ 5″; thorax opened; heart still beating; stoppage of both auricles and ventricles in systole, at 3′ 15″.

Experiment 83.—Large cat; secured; 0.6 strychniæ acetas rapidly injected into thyroid branch of common carotid; instantaneous struggle (not tetanic), and death; autopsy: heart in rigid systole; brain moderately injected; no venous engorgement.

Experiment 96.—Large cat. Chloroformed; 0.5 injected, as before (canula pushed forward to lumen of carotid trunk). Death instantaneous; brain anæmic.

As an appendix to this chapter I will add one experiment, which sustains the inference that the legitimate effect of strychnia is contraction and not dilatation of the pupil. In order to test this properly, it is necessary to eliminate the disturbing influence of the asphyxia, which was already done in Experiment 153, by maintaining artificial respiration. In that case the reader will recollect that the pupils were contracted in the free intervals. This factor can be more directly eliminated.

Experiment 193.—Full-grown rabbit. Division of both cervical sympathetic nerves; medium contraction of pupils as a result. 0.05 subcutaneously; first spasm at 1′10″; with the spasms the pupil became progressively more contracted, and at length reached a pin-hole size; it returned to its previous condition just before death, which occurred in 40′.

That the irritability of the retina might not be accused of having caused this contraction, I repeated this experiment in another rabbit (Experiment 307) whose optic nerves I had divided the day previous; the same result was observed as in Experiment 193.

IX. THE PATHOLOGY OF ACUTE STRYCHNIA POISONING.

The first question presenting itself in relation to this topic is, whether any accurate micro-chemical test for strychnia can be applied to the nervous tissues. My search for such a test was in vain; but I have accidentally discovered an appearance, which, although not sufficiently decided to admit of any mature conclusions being derived therefrom, may lead to further inquiry. In the cord of a large cat which had been poisoned by a large quantity of the alkaloid (Experiment 1), after immersion in pure bichromate of potash solution (1:100 water) a peculiar greenish tinge was observed in the pia and the grey substance of the cord. As no alcohol or glycerine had been brought in contact with the specimens, and as the bichromate is not reduced by undecomposed animal tissues, I am at a loss to account for this appearance on any other basis than a strychnia reaction. The greater quantity of strychnia in the vascular pia and grey substance would account for the greater intensity of the color here; in fact, the white substance proper, aside from the processes of the pia and the grey cornua, did not present the tint in question at all.

Microscopically, this green color was equally distributed in the cells, septa and neuroglia.

I have also found it impossible to test for the minimal quantities of the poison which are found in the various organs, *quantitatively*. I can only infer that the grey substance contains more than the white, from the fact that those portions of the nervous centres containing most grey substance gave the clearest reactions; thus the medulla oblongata shows it better than the cord. That this preponderance in the grey substance is not due to a special affinity, but to its greater vascularity, I have hinted above. Gay claims that there is more strychnia in the medulla oblongata than in the cord; and the fact that I have often found it here, when examination of the cord gave a negative result, speaks in his favor.

Qualitatively, I have found strychnia, when administered in large doses, in the olfactory lobes, retina, cerebro-spinal fluid, basal ganglia, cortex, crura, cerebellum, medulla, cord and peripheral nerves. In short, it is probably universally distributed through the nervous system.

Neither in freshly-prepared nor in hardened specimens could I discover the slightest anatomical change. The nerve fibres, the ganglion cells, the neuroglia and the white substance were ideally healthy. I am aware that others have described changes in the contours of the cells, destruction of the nuclei, and molecular alterations of the protoplasm, but there is not one of these appearances that cannot be referred either to imperfect observation or improper manipulation. I have employed sections of cord, obtained from animals dying in extreme tetanus, to demonstrate the normal anatomy of the parts. The softening noticed by other writers is either cadaveric or collateral to hemorrhages, or due to serous exudation from the over-distended blood-vessels, when occurring in cases of acute duration.

The vessels are uniformly stated by various writers to be engorged. Most of them correctly ascribe this engorgement to the asphyxia and muscular over-exertion, not to a local effect of the alkaloid. It therefore becomes a secondary result — not an essential feature of strychnia poisoning. This is borne out by the fact that animals dying suddenly with either no, or very few, convulsions, have a rather bloodless brain, while the longer the convulsions have lasted, the more intense does the venous engorgement of the nervous centres become. As an illustration, I append the autopsy record of some of the more suggestive experiments in this essay.

Autopsy of No. 153.—Heart half relaxed, lungs slightly congested, prevalently on the right side, on which the animal had lain during the experiment. Abdominal viscera of normal appearance; large veins filled with lake-colored blood; arachnoid fluid clear; surface of cord sections injected; sinuses moderately filled with lake-colored blood; cerebral veins of both convexity and base, spinal and vertebral veins, moderately filled; arteries of larger calibre empty; arterioles well filled; no capillary injection of brain. Microscopical examination of cord and medulla, as well as of superior cervical ganglion failed to show any change.

Contrast this with the ordinary result, as obtained from an unrecorded experiment: Dog. 0.06 subcutaneously; in typical convulsions for two hours,, with intervals; not observed after that period, and found dead eight hours after administration. Pupils in maximal dilatation, rigor mortis, lungs collapsed, ecchymotic, pleura costalis ecchymotic, ventricles of heart empty, left auricle same, right auricle and great veins filled to distention with dark-colored blood; liver, spleen and kidneys congested and soft; the blood runs profusely from the cut surface of these organs; bladder contracted and empty.

Arachnoid fluid tinged with blood; pia of cord, base of brain, and convexity intensely injected; veins and sinuses engorged. Hemorrhages had taken place at various points, chiefly sub-pial, but in one locality into the arachnoid space. One large coagulum had been poured out around, and had torn the radicles of the fourth cervical nerve; the grooves between the pons and trapezium, between the latter and the medulla proper, as well as the posterior perforated space, were obliterated by hemorrhages.

This picture is so similar to that found after asphyxia from strangulation, that its cause instantly suggests itself. It is not due to the strychnia primarily any more than the same venous engorgement found in tetanus, hydrophobia and epilepsy is due to the respective primary influences. That the heightened blood pressure in the arteries and the accelerated blood current may increase an already established engorgement — and thus the latter become transferred to the intermediate capillaries as a capillary stasis, produced during the final agony — does not militate against this view.

To obtain a perfect idea of the mode by which the venous engorgement is produced, it is desirable to observe its production in the living animal.

Experiment 185.—A half-grown dog is secured on the tray, and the obturator membrane divided so that the two longitudinal veins on its visceral side are not injured. This is accomplished by a crucial incision and cutting away the flaps piecemeal with a curved scissors. On now flexing the dog's head, the upper part of the cervical cord and the lower of the medulla oblongata become visible as far as the nodulus cerebelli. The surface of the columns is white, with delicate vascular rami; pulsatory excursions of arachnoid fluid invisible; respiratory excursions marked. The ventricular choroid plexus is rosy in hue, as also the ventricular floor and the cerebellar surface, though much lighter. Strychniæ acetas 0.015 was then injected under the nuchal skin. 22″, pallor of cerebellar cortex, vascularization of cord less patent; at 45″ this increases; the respiratory oscillations of arachnoid were marked. The choroid plexus now becomes redder, in contrast with the cerebellum, and a convulsion interrupts the observation momentarily. The head is forcibly flexed, but a stream of venous blood running from the cranial cavity obscures the view. As soon as this coagulates it is removed, and the apex of the ventricular floor is found injected, the choroid plexus purplish, and large vessels, previously invisible, are now seen in the pia mater. The purplish injection gradually fades during the next four minutes, but recurs during the next spasm, reaching a more intense degree than previously. This was repeated twice; on the last occasion there was another escape of venous blood between the cerebellum and medulla, during which the animal died. As long as the arteries could be observed, it was evident that they did not return to their normal calibre in the quiet interval.

Experiment 71.—Cat. Trephined and dura excised; glass plate inserted; received 0.06 the following day. Tetanus, as usual; no arterial engorgement observed prior to same, but more marked with each spasm, reaching its highest point in the terminal convulsion. Microscopical examination of medulla oblongata and occipital cortex: nerve elements healthy; capillaries filled with blood discs, whose outlines are distinct; agglutination in rolls frequent. Red corpuscles crowded in the adventitial and perivascular spaces; an increase of the round (lymphoid) bodies in the neuroglia.

I did not in my previous contradiction of the asserted pathological findings of recent writers take cognizance of the lesions which have been described as occurring with traumatic tetanus and hydrophobia, two conditions presenting many points of analogy to strychnia intoxication. Of the lesions described by Meynert in connection with the former affection, I shall have occasion to speak later. As to hydrophobia, Benedict has described "peculiar fatty or granular bodies" in that affection in Virchow's *Archives;* his figures clearly show the artificial nature of these bodies.

That the condition of the blood, as to quantity and quality, can have no influence in determining the tetanus, could have been inferred from the experiments of Salkowski, who produced tetanus as readily in frogs deprived of their blood, and having that fluid replaced by a saline solution as in normal animals. I have verified the latter experiments; an elegant variation of Salkowski's experiments consists in keeping the saline supply a constant one through a capillary glass tube, permitting the wound in the lower end of the divided ventral vein to remain open. The strychnia may be injected hypodermically, or better still, added to the saline solution.

A final dilatation of the arterioles and some capillaries can be often observed to take place just previous to death in the frog's web, the rabbit's mesentery, and pia mater. It is probably like the anenergy of the muscular system correspondingly observed, a symptom and result of over-excitation.

I refrain from appending a series of observations on frogs and toads confirming the conclusions just obtained, and would merely mention, that a deep injection and occasionally a hemorrhage under the velum of the fourth ventricle were noticed in every instance where the tetanus had lasted a long time. On microscopic sections of the medulla and cord of a turtle, I found numerous capillary hemorrhages, without alteration of tissue; the maximum of the change was in the spinal cord above the roots of the second cervical pair, and in the lower half of the medulla oblongata. The same was noticed in other animals, whether they had died of strychnia poisoning, or ordinary asphyxia; it has also been found in those dying in the status epilepticus. The localization of the hemorrhage is therefore doubtless due to mechanical factors.

X. THE PHYSIOLOGY AND PATHOLOGY OF CHRONIC STRYCHNIA INTOXICATION.

I have not been able to find any statements in the literature with regard to the experimental induction of chronic strychnia poisoning.* Schroeder Van der Kolk reports the example of a dog who was under strychnia four days, and finally recovered; and other observers have casually mentioned that frogs often remain in tetanus for several days, but none have, to my knowledge, made any systematic observations in this direction.

After numerous failures with the hypodermic method, I adopted the following procedure: A series of sixty-two specimens of *Rana leopardina* were placed in as many numbered glass jars. A record was placed with each jar, and enough water being allowed each frog to moisten the under surface of his body, a drop, or several drops (according to the size of the animal), was added from a standard solution of strychniæ acetas, containing 0.001 to the drop of water. The experiments were performed in the winter of 1877–78, in a permanently dark chamber, only occasionally illuminated by a candle, when the records were revised and the strychnia solution added. Cold and darkness proved valuable aids in maintaining the lives of these amphibians; the former factor for this special reason, that tetanus could be induced by lesser doses, and kept up for a longer time on the same dose in cold weather than in warm, according to my experience, thus verifying similar observations of Künde.

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*Since writing the essay, I have found that Vulpian had succeeded in this nine years ago.

Many of these frogs died on the fourth or fifth day, others, after having been in tetanus a longer or shorter time, escaped; fifteen survived to the twentieth and thirtieth day, and four lived forty-five days and longer.* There seem to be individuals of this species who have a greater amount of resisting power to the drug than others; it seems that those requiring but little strychnia and whose tetanus comes on gradually, have the best chances for recovery.

As soon as accelerated movements of the nostrils and flanks showed themselves, the strychninized water was poured off, and replaced by pure water, the tetanus following would last about twelve hours; as soon as it weakened, the strychnia solution was renewed. During the first eight days, the strength of the alkaloid had to be gradually increased, if the animal had been allowed to recover entirely from each attack; but if added while still under the influence of the earlier dose, it was kept to the same amount. After two weeks, it was found that the dose which when first given maintained tetanus twelve hours, now maintained it for two, three and even five days without renewal. I found it more difficult to maintain the tetanus during the first two weeks, than during the next two.

Frogs who escaped during the second week, and were recaptured some time after, showed no untoward symptom. No routine was adhered to strictly: the procedure was different for some individual cases.

Experiment 142.—*Rana leopardina.* November 8th; 0.001

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* Since writing the essay, I have succeeded in maintaining five frogs in tetanus for over forty days; one of these survived to the sixty-seventh day, and was intended for demonstration to the N. Y. Neurological Society, but being neglected, he was found, three days after, desiccated, having perished for want of water.

in water; four hours after flank and nostril movements spasmodic; five hours, hyoid contraction; he then occupied a drawn-together position, from which he frequently started, and the water was poured off. Tetanus developed at eight hours, with croaking; nine hours, maximal tetanus, croaking ceased, irritable; fourteen hours, recommenced croaking (augurs recovery). November 10th, A. M., animal irritable, occasional clonic shocks, pupils dilated. Strychnia renewed; four P. M., no tetanus; ten P. M., tetanus recommenced. November 10th, pupils moderately contracted; tetanus reaches an extreme degree; for six hours the animal is as rigid as a rod, and not expected to recover. November 11th, still in tonic spasm; pupils contracted. November 12th, tonic spasm occasionally gives way to clonic; croaking resumed. November 15th, A. M., still in clonic spasms, with occasional tonic spells. Strychnia renewed, P. M.; again in rigid spasm. November 14th, 15th, continued tonic spasm. November 16th, lively; relaxed, but irritable; jumps stiffly. Strychnia renewed; November 16th, full tetanus; the color of the animal is undergoing a change, the ventral yellow is becoming brighter; the cutaneous vessels are hyperæmic, especially noticeable on web. Observation imperfect up to November 27th, when the history of the 15th, 16th and 17th was repeated. November 30th, apparently dead; on opening body, heart still beating; all the internal organs, especially the omental fat-lobules and the brain well injected; the thalami and optic lobes greyer than normal; brain and medulla firm in consistency. From November 8th to November 30th, or out of 504 hours, this animal was known to have been in spasms for 298; of these, 218 hours represent one continuous period of tetanus; and it would have lived longer, doubtless, if it had not been opened under the erroneous impression that it was dead.

Experiment 246.—Middle-sized *Rana fontinalis*.

November 10th, tetanus throughout the day.
" 11th, " " " " recovering; added strychnia.
" 12th, " " " "
" 13th, " less pronounced.
" 14th, " and tremors; renewed strychnia.

November 15th, tetanus complete; added strychnia.
" 16th, " croaking; relaxation, P. M.; renewed strychnia, and did not change water.
" 17th, " throughout day complete.
" 18th, " " " "
" 19th, " " " "
" 20th, " " " "
" 21st, " " " " added strychnia.
" 22d, " " " "
" 23d, " " " "
" 26th, " anenergetic; animal stiff and extended, but continually agitated by tremors.
" 27th, " ditto.
" 28th, " ditto; tetanus relaxing; on being turned out of jar, and after passing out of the transitory tetanus, induced by the irritation, crawls clumsily, and in all its movements is decidedly ataxic.
" 29th, as yesterday; renewed strychnia.
" 30th, complete tetanus.
December 1st, " "
" 2d, " "
" 3d, " "
" 4th, recovering; added strychnia; P. M., tetanus.
" 5th, A. M., tetanus; symptoms of recovery; renewed strychnia.
December 6th, complete tetanus.
" 7th, " " renewed strychnia.
" 8th, " " tremors of a jactitating character; hyperæmia of integuments extreme.
" 9th, " "
" 10th, " "
" 11th, " "
" 12th, " "
" 13th, " "
" 14th, " "

December 15th, complete tetanus renewed; a frog of one-third the weight of the present one, immersed in the same solution, fails to show tetanus.

" 16th, recovering; pupils in most intense contraction; on being turned out of jar, walks in a clumsy, ataxic, and halting manner, muscles rigid. Tetanus recurred before strychnia was renewed.

" 17th, clonic spasms; strychnia renewed.

" 18th, recovering; animal permitted to rest, in order to study its gait; every now and again the hind legs would shoot out, and when fully extended would be found relaxed, thus differing from true tetanus. In jumping the frog frequently lands on his back, although free from spasms at the time.

" 19th, strychnia renewed; tetanus returns, of a tremulous character; pupils less contracted than yesterday, when it had no strychnia; from this time forward, it was observed that as a general thing, the increasing contraction of the pupils heralded recovery.

" 20th, tetanus continues; still more tremulous and anenergetic.

" 21st, Ditto.
" 22d, "
" 23d, "
" 24th, "
" 25th, "
" 26th, "
" 27th, " added strychnia.
" 28th, tetanus still more anenergetic.

" 29th, " still more so; the eyes have been firmly retracted for the last twelve days; the tetanus is becoming feebler, but strychnia not renewed.

" 30th, a feeble opisthotonos this A. M.; tremors increasing in intensity; found dead and relaxed in the afternoon.

This frog was under the continual influence of strychnia for fifty-one days.

The experiment and similar ones, are important as showing that in the course of chronic poisoning certain symptoms are developed, quite distinct from those observed in acute strychnia poisoning. The anenergetic character of the tetanus, it might be argued, was due to the muscular exertion protracted beyond physiological limits, and slight tremors similar to those noticed in protracted tetanus after a single dose might be thus explained. But the tremors observed in the last stage were too excursive to be attributed to this cause, and although unable to get a full registry of the curve, satisfied myself that it was quite distinct from Kronecker's "Ermüdungs-curve." They resemble rather the results of central disease, producing active irritation. Then, also, while the animal was recovering, for a day or so on two occasions, symptoms were noticed, referable to a morbid central irritation independent of the strychnia. These are the pronounced ataxia, the "spinal epilepsy" and the pupillary contraction. In other experiments, where animals had been allowed to recover after having been in tetanus for over thirty days, the "spinal epilepsy" was observed for four and six days after the tetanic symptoms had passed away, while the ataxia and pupillary myosis continued for weeks, until the animals died, or as one did, permanently recover. I regard the "spinal epilepsy" as such, and as distinct from the tetanus not only for this reason, and on account of its character, but, also, because the spasm in the hind legs was unassociated with trunk, head, eye, and fore leg spasm, as it would have been had it been a tetanic spasm. It could be brought on occasionally by pinching the hind feet, but not by irritating any other part of the body. I should state, however, that not in all frogs are all these symptoms produced to the same extent.

Altogether these symptoms suggest central changes, and it is noteworthy that the normally white tissues of the brain should have shown in places a greyish tinge. It is to be regretted that the preservation of the brain failed, while that of the cord is not complete enough for an examination at date.*

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* Unfortunately lost, since.

Probably the deficient energy of the tetanus at the end was due to the fact that the alkaloid had but a damaged nervous axis to work on.

Experiment 253.—*Rana leopardina*, kept in tetanus nine days; death. Autopsy: arterial hyperæmia of all organs; extravasation in muscular masses of left thigh; cord and brain firm; increase of round nuclear bodies in neuroglia; nerve cells and nerve tubes entirely healthy. Brachial and sciatic nerves highly injected; no changes histologically.

Experiment 250.—*Rana leopardina*, maintained in tetanus for four successive periods of three, eight, seven and eleven days respectively, interrupted by imperfectly tetanic periods of from six to twenty-four hours. On recovering from the last dose the animal was restless for three days, then it was observed that the right eyeball protruded less than the left, the pupil of the former being in maximal contraction, the latter normal (medium dilatation). The gait became progressively more ataxic up to the fifth day; tremors and "spinal epilepsy" marked. From this time on there was a stand-still in the symptoms, the frog was indisposed for exertion, but remained crouched in a dark corner. If handled, the tremors came on. On the eighth day after ceasing administration, it died asthenic.

Besides affecting the central nervous system, chronic strychnia poisoning affects also the vaso-motor; whether this be due to the muscular over-strain, or a direct paralysis of the ganglia, I am not prepared to state. To show that like the vasomotor symptoms of acute poisoning, they are independent of the cord, I in

Experiment 287, pithed the cord of a frog, that had been in tetanus twelve days, and divided the vagi of both sides. Death seven hours after operation; injection of skin persists, no œdema.

In the case of the spinal cord of frog No. 142, I had the good fortune to discover destructive lesions of the nervous system, and thus to base the peculiar symptoms of chronic strychnia poisoning upon a pathological foundation. As might have been anticipated, these lesions were secondary results.

The specimen to be described had been hardened in bichromate of potash, after having been in a one-half per cent. solution of chromic acid; it was cut in a hand microtome and stained in carmine and hæmatoxylin, then after the usual routine, examined in clove-oil or glycerine.

The section showing the most intense changes was obtained from above the origin of the first cervical nerve; the cord here shows the commencing type of the medulla oblongata. Both posterior white columns were the seat of scattered foci of disease. There were two smaller areas on the right side, which were confluent in lower sections, and which nowhere reached the periphery; on the left side there was a single area which reached the periphery. The changes consisted in an absence of the nerve-tubes normal to the locality, their place being occupied in all three foci by a molecular and granular material, without any very pronounced structure. In addition, there was some granular and crystalline pigment present. In the right patch every transition could be observed between scarcely altered blood-discs and black angular hæmatoidin crystals. A transparent crystalline body, colorless, and with imperfect angles (possibly cholesterin). These various bodies were crowded closely together, the tissue between them was amorphous, and stained but little in carmine. Several spider cells, with marked processes, were visible in the periphery; and with these, a semi-fibrillated connective tissue, with very few nerve-tubules. This tissue contained various oblong meshes, filled with neuroglia-nuclei-like bodies in great numbers. They stained deeply in carmine.

In other segments, diffuse pigmentation, with a slight hypertrophy of the neuroglia, constituted the sole change. It could be traced up as far as the cerebellum, and down to below the roots of the great brachial nerve; beyond these points no good sections were obtainable. How far other appearances noted are to be considered pathological, I am not prepared to say, until the variations of the batrachian cord shall be better studied under normal circumstances.

Although these changes are undoubtedly the result of past hemorrhages and inflammatory stasis, and are, therefore, due to the asphyctic engorgement and later vaso-motor paresis, rather than to the local effects of the strychnia, they assume some importance when correlated with the symptoms manifested *intra-vitam.*

The white softening, which I have found in some other cases of chronic strychnia poisoning, and also in frogs dying after having been in extreme tetanus for several days, is not always the collateral softening of hemorrhages, or of oedema from engorgement. I have found it to be distinctly fascicular in its distribution; and am inclined to consider it a myelitis, the result of muscular over-exertion—such a myelitis as Leyden presumes to occur in the human subject, without exudation and hyperæmia.

The sequence of these various pathological conditions, I consider as following two lines in as many groups. First group.—Extreme tetanus, with muscular over-exertion, followed, sooner or later, by simple softening of cord; death. Second group.—Engorgement of cord, from asphyxia and strain; stasis and diapedesis of lymphoid bodies in certain foci; hemorrhage and tissue destruction in others; active hypertrophy of connective tissue in both localities, with pigmentary metamorphosis of clot in the latter; death after a considerable period, or partial recovery. All the lesions most intense in the posterior columns.

Nowhere was there any evidence that either the nerve fibres or ganglion cells were primarily diseased.

The development of spider cells, in great numbers, I have also noticed in the cord of a dog that had recovered from two strychnia intoxications, separated by an interval of eight days.* Meynert found the same appearance in the cords of hydrophobic and tetanic individuals; and it is very likely that the same appearance will be found in protracted cases of human strychnia poisoning.

The conclusion naturally follows, that there must be some factor common to all three conditions, which results in the same pathological change, and that the latter does not depend on the specific nature of the irritant. That factor is, as we have stated, the vascular engorgement.

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*It is needless for me to state that chronic strychnia tetanus is not possible in warm-blooded animals.

Summing up these results, we find, first, that frogs can be maintained in strychnia tetanus for from one to eight weeks; that at the end of the longer periods they manifest symptoms of a central affection, and that lesions are found in the cord, partly as an insular sclerosis, partly as a hemorrhagic and non-hemorrhagic myelitis, to account for those symptoms.[*]

Aside from their purely physiological interest, these experiments have a therapeutical one, in so far as they show that in the beginning the strychnia has to be occasionally increased, but that later it can be decreased, and given at rarer intervals, in order to keep up the physiological effects. That the pathological effects of chronic strychnia poisoning constitute a warning to those who indulge in the routine administration of the remedy, is evident; and experience has already condemned this practice.[†]

XI. THE RELATION OF STRYCHNIA TO ITS ANTIDOTES.

Although the question of the antidotal effects exercised by certain drugs, does not properly fall within the limits of this essay, I propose to briefly review this aspect of the question, in order to make some inferences as to the action of strychnia itself.

It is stated by some authors that hydrate of chloral, by others that the constant galvanic current, by still others that curare is an antidote to strychnia; and that cases of poisoning treated by these agents, with the assistance of quiet and darkness, can recover. The latter statement is undoubtedly true. It remains to be seen in how far this beneficial influence is truly antidotal, or whether it consists in the obliteration merely of certain symptomatic results.

Several problems enter into the discussion of this question, which complicate it considerably. In the first place, let us assume that two substances are strictly antidotal, and will in given relative doses, neutralize each other's effects entirely. In order to do this, it is evident that their administration must be so timed (at least with regard to neurotics), that the height of the effect of the one drug will be synchronous with the height of the effect in the other. These conditions it is almost impossible to comply with; and it may happen that instead of neutralizing each other, the toxic effects of two alkaloids may virtually be added together.

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[*] A proliferation of the epithelium has been noted around the central canal in one specimen.

[†] As an example, I may quote the case of a lady seen by myself, in consultation with Dr. Skinner, of this city, in which I made the diagnosis of a tumor, pressing upon the cord at the vertebra prominens. Here as little as $\frac{1}{100}$ of a grain of strychnia produced intense aggravation of the symptoms before I saw the case.

I have found that chloralized rabbits show the toxic effects of large doses of strychnia as rapidly as non-chloralized animals; that moderately large doses produce tetanus in spite of chloral, although the effects of small doses are annulled. My experience with the galvanic current is the same.

It is, therefore, my opinion that these and other antidotes act favorably by suppressing certain of the results of strychnia at the periphery, but that they do not neutralize the essentially lethal action of the alkaloid, which it exercises on the nerve cell protoplasm. *Per se*, strychnia kills the nerve cell, as it is able to kill other complex protoplasmic bodies (leucocytes).

We may state, that the galvanic current alters the electrotonus of the cord, so as to prevent the transmission of the tetanizing influence to the periphery; that curare paralyzes the intra-muscular nerve-ends, and renders it impossible for the muscle to respond; and that chloral blunts the sensibility and counteracts the transmission of centripetal irritations; but we cannot assert that any of these agents neutralizes the central influence of strychnia. The drug which, in my opinion, approaches most closely to the ideal of an antidote, is conium.

The three remedies first mentioned, are no more true antidotes than are darkness, quiet, and a moderate temperature, or any other suppression of peripheral irritation. I should add, however, that because irritation provokes strychnia spasms, it does not follow that without irritation there will necessarily always be fewer spasms. When large doses are given to two frogs of the same size, the one frequently irritated will cease to respond, after a time, altogether; such spasms as occur then, come on spontaneously. In the other, the spasms will be fewer at first, and progressively become more intense, frequent and permanent. Both will die at about the same time, and have had the same sum total of spasms.

The therapeutical agents mentioned have no influence in abolishing the sequels of chronic strychnia poisoning.

In proposing remedies for strychnia poisoning, the tetanus has chiefly been regarded, and sight lost of the fact, that strychnia in large doses is an essential poison to the nervous system, whether convulsions occur or not.

SUMMARY.

1. Strychnia is a poison to all forms of animal life.
2. Strychnia exercises its influence upon animals by affecting the central nervous apparatus and the vaso-motor system, but it can act fatally on animal forms possessing neither of these systems, and must therefore be considered as acting lethally on all complex tissues.
3. Strychnia acts on the grey matter, on all grey matter alike, and affects both its sensory and motor elements.
4. The white nervous matter and the peripheral nerves play but the passive rôle of conductors.
5. Strychnia does not affect the nerves or muscles locally.
6. It affects the peripheral end organs of special sense locally.
7. Strychnia produces tonic spasm in all vertebrates.
8. In higher vertebrates, clonic spasms are added.
9. This difference between higher and lower vertebrates in this respect is probably due to the difference of the nervous system.
10. The clonic spasms are more intense, *cæteris paribus*, in smaller than in larger animals.
11. In higher animals the spasms are due to the action of the alkaloid on the axial parts of the nervous system, the pons, medulla and cord.
12. The maximum of the tetanizing influence is intra-cranial, and thence it gradually diminishes toward the posterior extremity of the cord.

13. Strychnia kills the lower vertebrates directly by nervous exhaustion, the higher, as a rule, by asphyxia and venous congestion of the nervous system in addition. In very large doses it is directly lethal to the nervous tissues.

14. Its vaso-motor effect is to increase the blood pressure, and the rapidity of the blood current, by contracting the arterial vessels. This effect is independent of the central nervous system.

15. Its effect on the heart is to augment the systole and prolong the diastole; the heart may cease acting by tetanic rigidity in any stage. These effects are produced first by the action of the alkaloid, on the local ganglia of the heart; secondly, through the pneumogastric nerve.

16. In large doses, cortical (epileptiform) spasms are presumably produced.

17. Strychnia is present in every organ of the body, after administration; it is found in all parts of the brain, cord and nerves.

18. It is in greater quantities in the grey than in the white nerve tissues.

19. It produces no visible changes either in the nerve fibres or nerve cells, whether given for a short or a long period.

20. Lesions are found after death from strychnia, which are not due to its direct local effect, but to secondary results.

21. Chronic permanent lesions are produced in the course of chronic strychnia tetanus, which are also referable to secondary influences.

22. There is no true antidote to strychnia, although various agents which diminish reflex excitability, and paralyze the muscles, or alter the tonus of nerve fibres, may enable an animal to survive the effects of otherwise fatal doses. But these means fail with larger doses.

23. Strychnia increases the reflex excitability, but not all strychnia spasms are due to this factor: some depend upon direct irritation of the motor cells.

24. As with other irritant toxic agents, the lethal effects are preceded by a stage of functional stimulation.

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